REMARKS

The present application is directed to novel compositions and methods comprising therapeutic delivery compounds. The compounds are particularly suited for the effective delivery of genetic matter and other compounds to the interior of cells. Claims 1-42 were pending prior to the issuance of the October 10, 2003, Office Action. Following entry of this amendment claims 1-42 will be pending. Claims 1, 5, 8-9, 13, 16-17, 19, 23, 26-27, 31, 33, 38 and 41-42 are amended herein. No new matter is added and support for the amendments is found throughout the specification.

Priority

In the October 10, 2003, Office Action the Examiner rejected the claim for priority by the Applicants to their earlier disclosed applications. Schmolka (J. Am. Oil Chemist Soc. 54:110-116 (1977)) (previously provided) teach the synthesis of block polymer non-ionic surfactants including poloxamines, see Figure 4. Schmolka is incorporated by reference in both priority documents 08/138,271 (hereinafter the '271 application (see page 17) and 07/673,289 (hereinafter the '289 application (page 23, lines 13-17). The Examiner rejected the Applicants' request for priority stating that the '271 application only recited the polyoxyethylene-polyoxypropylene (POE-POP) linear copolymers. Applicants respectfully submit that the **'289** application recites octablock copolymers with a polyoxypropylene portion and a molecular weight of approximately 5,000-7,000 Daltons of the total weight of the octablock copolymer. The polyoxyethylene portion of the total octablock copolymer constitutes between approximately 10-40%, and the POP portion accounts for 60-90% of the total weight of the octablock copolymer.

In addition to an octablock copolymer with a molecular weight of 5,000-7000 Daltons, the '289 application also recites that the octablock copolymer may contain as little as 5% POE and 95% POP as percentages of the total weight of the octablock copolymer (see page 20, lines 3-20). These octablock polymers may be used as an adjuvant in the delivery of therapeutic agents. Applicants also submit that claimed nucleic acid sequences, selected from ribozymes, antisense oligonucleotides, triplex DNA compounds are disclosed in the '271 application and are therapeutic agents. Furthermore a composition comprising an expression

vector encoding a gene product which is expressed by the host may act as an immunomodulating agent. The '271 application states that the present invention "relates particularly to compositions and methods of treating infectious diseases and genetic disorders through gene therapy and intracellular deliveries of antisense oligonucleotides or other nucleic acid sequences." (page 6, lines 1-4). The '271 application also incorporates by reference the synthesis of poloxamines (Schmolka). Applicants respectfully submit that the priority applications disclose the claimed nucleic acid sequences and octablock copolymers and are therefore correctly claiming priority. Applicants assert they have established a clear claim of priority in which both octablock copolymers and nucleic acids sequences are disclosed, and therefore request the priority date of at least October 15, 1993 to be allowed.

Claim rejections under 35 U.S.C. § 112, 2nd paragraph

In the October 10, 2003, Office Action the Examiner rejected claims 1-38 under 35 U.S.C. 112, second paragraph for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner stated "that the intended scope of the nucleic acids intended to be embraced is unclear." Applicants respectfully traverse the rejection and assert that the amended claims define one or more nucleic acid sequences. Applicants have amended the nucleic acid sequences included in the Markush group. Applicants submit that one skilled in the art would understand the phase "nucleic acid sequences" to include DNA polymers and RNA polymers in the various physical forms known in the art. The amended claims recite a nucleic acid sequence selected from the group consisting of: oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes, or a mixture thereof. Support for the use of these terms can be found throughout the specification. Accordingly, Applicants respectfully submit they have overcome the rejection under 35 U.S.C. 112, second paragraph and request its withdrawal.

Claim rejections under 35 U.S.C. § 102

In the October 10, 2003, Office Action the Examiner rejected the claims 1-5, 8-13, 16-23, 26-31, 33-36 and 38 as anticipated by Lemieux et al., U.S. 6,359,054 (hereinafter "Lemieux et al.") under 35 U.S.C 102(e). The Examiner stated that Lemieux et al. teach

methods of delivering to an animal a composition comprising octablock copolymers and nucleic acids (e.g. claim 13). The nucleic acid can be an expression vector, antisense, ribozyme or oligonucleotide (see col 21, lines 15-29).

Applicants respectfully traverse the rejection and submit that Lemieux et al. is not a 35 U.S.C. 102(e) anticipatory reference. As mentioned above, Applicants believe that this application should be entitled to a priority date of at least October 15, 1993. Therefore, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. 102(e).

In addition the Examiner states that Lemieux et al. disclose octablock copolymers T1101, T1301, T1501, T110R1, T130R1 and T150R1 (col 14, lines 34-36 and 54-64). Appliants respectfully submit that lines 54-62 of column 14 do not describe the above said Tetronics, but describe **linear POE-POP block polymers** of formula XXVI. Lines 62-64 (formula XXVII) refer to octablock copolymers comprising a POP portion with a molecular weight of less than 2200. In contrast, Applicants submit that the pending claims refer to octablock copolymers with a POP portion of approximately 5,000-7,000 Daltons.

In addition, the octablock copolymers presented in column 15, lines 11-18, recite a POP portion with a molecular weight of 5500 Daltons. Applicants submits that claims 4 and 22 recite a POP portion of the octablock copolymer with a molecular weigh of approximately 5220 Daltons. Similarly, the reverse octablock copolymers presented in column 15, lines 25-31, recite a hydrophobic weight of 5700 Daltons or 6700 Daltons. Lemieux et al. recite an average molecular weight, however, without a given standard deviation, it is unclear what the molecular weight is for each copolymer. Nevertheless, the pending claims 12, 30 and 36 cannot be anticipated by Lemieux et al. as Applicants recite a total octablock molecular weight of 5,220 Daltons, which is not taught or suggested by Lemieux et al.

Applicants respectfully submit that the Lemieux et al. is not an anticipatory reference and furthermore does not recite <u>all</u> the claimed limitations. Accordingly, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. 102(e).

Claim rejections under 35 U.S.C. § 103 rejections

In the October 10, 2003, Office Action claims 1, 6, 7, 9, 14, 15, 19, 24-25,27, 32, and 37 were rejected under 35 U.S.C. 103(a) as being unpatentable over Lemieux et al. in view of

Emanuele et al. U.S. 5,656,611 (hereinafter "Emanuele et al."). The Examiner stated that Lemieux et al. teach methods of delivering to an animal a composition comprising octablock copolymers and nucleic acids (e.g. claim 13). The nucleic acid can be an expression vector, antisense, ribozyme or oligonucleotide (see col 21, lines 15-29). Lemieux et al. does not teach a composition comprising both 0.1-5% by weight of a surfactant and 0.5-5% by volume of a low molecular weight alcohol.

According to the Examiner, Emanuele et al. teach that surfactants such as Tween 80 and ethanol may be added to emulsions of non-ionic block polymer composition comprising nucleic acids, (see col 11, lines 39-58). The Examiner concluded it would have been obvious to one skilled in the art to add surfactants and low molecular weight alcohol to the composition of Lemieux et al. in order to stabilize the emulsions.

Applicants respectfully submit that Lemieux et al. and Emanuele et al. are not proper prior art references. Both applications were filed after the priority applications disclosed in the current specification to which the Applicants correctly claim priority (see discussion above for details). Applicants respectfully submit that the priority claim of at least October 15, 1993, overcomes the rejection under 35 U.S.C. 103(a) and request its withdrawal.

In addition, Applicants respectfully submit that the cited reference, U.S. Patent 5,656,611, issued on August 12, 1997 was **not** issued to Emanuele et al., but rather Kabanov et al. Given the information provided by the Examiner in the Office Action, Applicants have tried to clarify the rejection raised by investigating the cited Kabanov et al. patent application (Col 11, lines 39-58; and claims 3,5, and 6). Kabanov et al. fail to teach or suggest that Tween 80 and low molecular weight alcohol may be added to emulsions of non-ionic block copolymer compositions comprising nucleic acids. Accordingly, Applicants respectfully submit that they have, to the best of their ability, responded to the Examiners' rejection under 35 U.S.C. 103(a) and request its withdrawal.

In addition, Applicants respectfully request withdrawal of the finality of the October 10, 2003, Office Action in view of the confusion in the Office Action regarding U.S. 5,656,611, which appears to be issued to Kabanov et al. rather than Emanuele et al. Without the correct patent details, Applicants are unable to ascertain the Examiner's rejection.

Claims 1, 2, 5, 8, 17-20, 23 and 26 were rejected under 35 U.S.C. 103(a) as being unpatentable over Pahlson et al. (Acta Pathol. Microl. Immunol. Scand. B. (1986)) (hereinafter "Pahlson et al.") in view of Woodard et al. (Laboratory Animal Science (1989) (hereinafter "Woodard et al."). The Examiner stated that Pahlson et al. teach a method of inducing an immune response in a mouse by administering **whole bacteria** emulsified in Freund's compete adjuvant. The Examiner stated that whole bacteria are considered to comprise expression vectors comprising sequences that can alter the function of nucleic acids. Further, whole bacteria would also be considered to comprise ribozymes as part of their ribosomes, as well as antisense oligonucleotides. Pahlson et al. do not teach octablock copolymers.

The Examiner stated that Woodard et al. teach that the octablock copolymer T1501 is equivalent to Freund's complete adjuvant for the purpose of stimulating antibody production. The Examiner concluded it would be obvious to one of ordinary skill in the art at the time of the invention to substitute the T1501 octablock copolymer of Woodard et al. for the Freund's complete adjuvant of Pahlson et al. and that one would be motivated to do so because Woodard et al. teach that T1501 and Freund's complete adjuvant are equivalent in the art of stimulating antibody production: therefore the invention as a whole was *prima facie* obvious.

Applicants respectfully traverse the Examiner's rejection. Pahlson et al. disclose the induction of an immune response via the use of hybrid cell lines producing monoclonal antibodies and utilizing whole bacteria as antigen immunization of DBA/1J mice. The bacterial antigen was harvested, washed, diluted and then emulsified with Freund's complete adjuvant. A selected amount of the emulsion was administered to the mice. Pahlson et al. clearly disclose the use of **whole bacteria** extracts. Such material would include all genomic and sub-genomic material, as well as other cytoplasmic matrix constituents (e.g. cell wall, plasma membrane, inclusion bodies, and the like). In contrast, the pending claims recite a composition comprising one or more nucleic acid sequences selected from the group consisting of: oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes or mixtures thereof. The recited compositions do not comprise whole bacteria (i.e. both genomic and non-genomic material). Applicants respectfully submit that the use of

whole bacteria as an immune response-inducing material is not recited by the claims and therefore Pahlson et al. in combination with other prior art references cannot properly render the invention as a whole *prima facie* obvious.

Claims 3, 4, 9-13, 16, 21-22, 27-31, 33, 35-36 and 38 were also rejected under 35 U.S.C. 103(a) as being unpatentable over Pahlson et al. (hereinafter "Pahlson et al.") and Woodard et al. (hereinafter "Woodard et al.") as applied to claims 1,2,5, 8, 17-20, 23 and 26 above, and further in view of Jansen et al. (hereinafter "Jansen et al.") (U.S. 4,902,500, issued 2/20/90).

The Examiner stated that Pahlson et al. teach a method of inducing an immune response in a mouse by administering **whole bacteria** emulsified in Freund's compete adjuvant. The Examiner also stated that whole bacteria are considered to comprise expression vectors comprising sequences that can alter the function of nucleic acids. Further, whole bacteria would also be considered to comprise ribozymes as part of their ribosomes, as well as antisense oligonucleotides. Pahlson et al. do not teach octablock copolymers.

The Examiner also stated that Woodard et al. teach that the octablock copolymer T1501 is equivalent to Freund's complete adjuvant for the purpose of stimulating antibody production. The Examiner concluded it would be obvious to one of ordinary skill in the art at the time of the invention to substitute the T1501 octablock copolymer of Woodard et al. for the Freund's complete adjuvant of Pahlson et al. and that one would be motivated to do so because Woodard et al. teach that T1501 and Freund's complete adjuvant are equivalent in the art of stimulating antibody production: therefore the invention as a whole was *prima facie* obvious.

Applicants respectfully traverse the rejection for the following reasons. Pahlson et al. disclose the induction of an immune response via the use of hybrid cell lines producing monoclonal antibodies and utilizing whole bacteria as antigen immunization of DBA/1J mice. The bacterial antigen was harvested, washed and diluted and then emulsified with Freund's complete adjuvant. A selected amount of the emulsion was administered to the mice. Pahlson et al. clearly disclose the use of **whole bacteria** extracts. Such material would include all genomic and sub-genomic material, as well as other cytoplasmic matrix constituents (e.g. cell wall, plasma membrane, inclusion bodies, and the like). In contrast, the pending claims recite

a composition comprising a nucleic acids sequence selected from the group consisting of: oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes or mixtures thereof. The recited compositions do not require whole bacteria (i.e. both genomic and non-genomic material). Applicants respectfully submit that the use of **whole bacteria** as an immune response inducing material is not recited by the claims and therefore Pahlson et al. in combination with other prior art references cannot properly render the invention as a whole *prima facie* obvious.

In addition, Jansen et al. teach stable antibody preparations containing a mixture of at least one polyoxypropylene-polyoxyethylene block copolymer **and at least one phospholipid** (abstract). Applicants' pending claims are directed to compositions comprising octablock copolymers and one or more nucleic acid sequences selected from oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes, or mixtures thereof; and related methods of delivering these compositions to an animal in the **absence** of a phospholipid. Therefore, Applicants respectfully submit that Jansen et al. fail to teach or suggest the claimed compositions. For at least the above reasons, Applicants respectfully submit they have overcome the *prima facie* rejection under 35 U.S.C. 103(a) in view of Pahlson et al., Woodard et al., and Jansen et al. and courteously request its withdrawal.

Claims 1-5, 8-13, 16-18, 20-22, 28-30 and 34-36 were rejected under 35 U.S.C. 103(a) as being unpatentable over Kabanov et al. (U.S. Patent, 5,656,611, issued 8/12/97). The Examiner stated that Kabánov et al. teach compositions comprising polynucleotide and octablock compositions having molecular weights and relative amounts of POP and POE overlapping the instant claims. (abstract, col 7, lines 23-col 8, line 11). The Examiner concluded that the inventions as a whole was *prima facie* obvious because the molecular weight ranges specified by the current application would have been obvious at the time of the invention to one skilled in the art.

Applicants respectfully traverse the Examiner's rejection of *prima facie* obviousness. As described in the priority section above, Applicants submit that they have disclosed the claimed limitations in the referenced priority documents 08/138,271 and 07/673,289. Applicants respectfully submit that the composition comprising of an octablock copolymer (with the claimed characteristics) and one or more nucleic acids sequences is disclosed and

entitled to a priority date of at least October 15, 1993. As such, Kabanov is not a proper prior art reference and cannot therefore establish a case of *prima facie* obviousness.

In addition, Kabanov et al. does not teach the precise limitations of the pending claims in respect to the molecular weight of the POP portion of the copolymer, or the overall percentage of POP versus POE. These characteristics are important to the functionality of block copolymers in general, including octablock copolymers. It is well established in the art (see Schmolka) that the physical property relationships which depend upon variation in the hydrophobe molecular weight and variation in the hydrophile-hydrophobe balance are shown to be similar in each series of block copolymers (e.g. Pluronic, Tetronic, Pluradot and Pluronic-R) but differ from one copolymer (e.g. T1301) to the next, in any one series (e.g. T1501). For instance, increasing the overall percentage of POP in the total octablock copolymer results in an increase in the hydrophobocity of the molecule and therefore an overall decrease its water solubility. Similarly, if the percentage of POE increases over the total weight of the octablock copolymer then the solubility of the molecule will also increase. Applicants respectfully submit that the functionality of the copolymers cannot be construed as equivalent amongst any one series (e.g. Tetronic) or else there would be no need in the art, or commercially, for a multiplicity of Tetronic polymers.

Furthermore, Kabanov et al. disclose polynucleotide compositions comprising a polynucleotide or nucleic acid molecule which has been covalently modified, and an octablock copolymer, **and at least one polycation segment which is a cationic homopolymer, copolymer, or block copolymer**, which is the reaction product of at least three amino containing monomers, or quaternary salts thereof, as demonstrated in Example 11. In contrast, the compositions of the instant claims do not require a cationic homopolymer or block copolymer. Applicants submit that for the above reasons, Kabanov et al. cannot establish a proper *prima facie* case of obviousness. Accordingly, Applicants respectfully submit they have overcome the rejection under 35 U.S.C. 103 (a) and request its withdrawal.

CONCLUSION

The foregoing is submitted as a full and complete Response to the Final Office Action mailed on October 10, 2003. No new matter is added by these amendments. For at least the reasons given above, Applicants respectfully submit that the pending claims are enabled, fully described, definite, novel and non-obvious. Accordingly, Applicants submit that the claims in the present application are in condition for allowance, and such action is courteously solicited.

A check for additional independent claims is enclosed. No additional fees are believed due; however, the Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, to Deposit Account No. 11-0855.

The Examiner is invited and encouraged to contact the undersigned attorney of record at telephone number listed below, if such contact will facilitate an efficient examination and allowance of the application.

Respectfully submitted,

Sima Singadia Kulkarni
Reg. No. 43,732

KILPATRICK STOCKTON LLP
1100 Peachtree Street, Suite 2800
Atlanta, Georgia 30309
Telephone: 404-815-6500
Our Docket No.: 19720-0625 (42896-261843)